CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-262

STATISTICAL REVIEW(S)

Statistical Review

NDA#	21-262
Name of Drug:	Brimonidine-Purite 0.15% topical ophthalmic solution
Applicant:	Allergan, Inc.
Indication:	Lowering intraocular pressure (IOP) in patients with open angle glaucoma and/or ocular hypertension
Documents Reviewed:	Vol. 1.1, 1.98, 99, 110-158/received on June 30, 2000
Medical Reviewer:	Jennifer Harris, MD
Statistical Reviewer:	Qian Li, Sc.D.
Dates of Review:	July-October, 2000

I. Introduction:

In this NDA, the sponsor pursues marketing approval of brimonidine-purite 0.15% topical ophthalmic solution (BPOS 0.15%) applied topically to the eye three times daily in lowering intraocular pressure (IOP) in patients with open angle glaucoma (OAG) and /or ocular hypertension. BPOS was a new formulation of brimonidine tartrate, which was the active drug substance of Alphagan (brimonidine tartrate ophthalmic solution 0.2%). The difference was in that BPOS 0.15% was preserved with Purite, rather than bezalkonium chloride. The purpose of this NDA was to demonstrate that BPOS 0.15% was safe and as efficacious as its original formulation Alphagan.

For efficacy evaluation, two identically designed double-blinded, active controlled pivotal studies (190342-007 and 190342-008) (referred to as Studies 7 and 8 later in this review) were conducted to determine the safety and efficacy of BPOS 0.15% and 0.2% in controlling IOP for patients with OAG and/or ocular hypertension.

This statistical review focuses on issues of the efficacy aspect in comparing BPOS 0.15% or 0.2% with Alphagan by treating patients with elevated IOP. The two pivotal studies had presented convincing efficacy results in treating IOP for patients with OAG and/or ocular hypertension. No major statistical issue has been identified.

II. Study Design and Statistical Methodology:

The two pivotal studies (Studies 7 and 8) for efficacy evaluation were identically designed Phase III studies that were conducted within United States. Both studies were multicenter, double-masked, randomized, parallel-group, and active-controlled studies in comparing the safety and efficacy of BPOS 0.15% or 0.2% to Alphagan. Both treatments were administered TID. Patients at least 18 years of age with IOP between 22 mm Hg and 34 mm Hg in each eye and asymmetry of IOP not greater than 5 mm Hg were recruited into studies. Patients were randomly allocated to 1 of the 3 treatment groups. Patients were treated bilaterally. The duration of trials was up to 1 year.

Study visits included a prestudy visit, baseline visit, and follow-up visit at Weeks 2 and 6 and Month 3. Additional visits were scheduled at Months 6, 8, and 12.

1. Efficacy evaluation:

IOP, the primary efficacy variable, was measured using a [redacted] applanation tonometer at Hours 0, 2, 7, and 9 at Day 0 (baseline), Week 6, Months 3, 6 and 12 or exit. IOP was measured at Hours 0 and 2 at Week 2 and Month 9.

Primary efficacy endpoints:

Based on the sponsor's statistical analysis plan, average IOP from both eyes were used in analyses. The average change in IOP for a patient was calculated by computing the change from baseline separately for each eye, then taking an average of the changes from both eyes. Three-month data was used for efficacy evaluation in this NDA. A mean decrease in IOP of at least 3 mm Hg from baseline was considered to be clinically significant. Mean IOP without subtracting the baseline was also evaluated.

Secondary efficacy variables:

Clinical Success (assessed by investigator): At Month 3 visit, the investigator was asked to determine if the study treatment was clinically successful, i.e., would the same treatment, if it was available, be considered for continuation after a patient completed the study.

Patient satisfaction questionnaire: At each follow-up visit a patient satisfaction and patient comfort question was asked. The question was that overall, how satisfied have you been with your most recent/study eye drop. Seven-point ordinal scale response was obtained.

2. Analysis populations:

Intent to treat population included all randomized patients. Per-protocol analysis included patients who met the protocol entry criteria for efficacy evaluation, received study medication, and had at least 1 follow-up visit.

3. Statistical Analyses:

Intent-to-treat with last observation carried forward and per protocol analyses were the co-primary analyses for IOP, the primary efficacy variable. Continuous variables including the primary efficacy variable were analyzed using ANCOVA approaches.
Ordinal categorical variables were analyzed using the Kruskal-Wallis and Wilcoxon rank-sum tests. Nominal categorical variables used Fisher's exact test, Pearson's chi-square test, or Cochran-Mantel-Haenszel (CMH) methods.

Closed testing procedure was used to adjust non-inferiority and superiority analyses, i.e., the same alpha level was used for both the non-inferiority and superiority analyses.

The definition of noninferiority was that the majority of the confidence intervals were within 1.0 mm Hg, and all confidence intervals were within 1.5 mm Hg. The new formulation would be considered superior to Alphagan if the difference in IOP lowering effect were greater than 1.5 mm Hg at all measurements. (Agreement between the sponsor and the FDA on Oct. 6, 1999)

4. Subgroup analysis:

Analyses of IOP were evaluated in subgroups created by the following variables: age, sex, race, iris color, and diagnosis for the primary efficacy variable IOP. Subgroup analyses were performed by combining both Studies 7 and 8.

5. Multiplicity:

The sponsor provided the following strategies in handling multiplicity issues occurred in this NDA.

ITT and per protocol analysis: both populations were analyzed to demonstrate consistent results for the primary efficacy variables. No adjustment of statistical significance level was made.

Multiple time points: agreement was reached between the sponsor and the FDA for the analysis of multiple time points. The requirement for non-inferiority was the differences between treatments which should be no greater than 1.0 mm Hg at majority of times and 1.5 mm Hg at all times for two sided 95% CIs.

Reviewer's comment: 10 time points were used to compare the efficacy among treatment groups. The criteria agreed between the sponsor and the FDA can provide consistent and convincing results across the time points assessed and can be quite conservative in protecting decision error, although there was no easy way to calculate the type I error rate given unknown correlation structure across different time points. Intuitively, there was no need to adjust type I error rate in a more conservative way.

Multiple comparisons among three treatment arms: stepwise comparisons were used. First the comparisons of each BPOS 0.15% and 0.2% versus Alphagan were examined. Then, if both BPOS concentrations were not inferior to Alphagan, the comparison of the two concentrations would be tested.

Reviewer's comment: For the comparisons of BPOS 0.15% or 0.2% versus Alphagan, closed testing procedure was applied in this review. That was to compare BPOS 0.2%

versus Alphagan first, if BPOS 0.2% was non-inferior to Alphagan, the comparison between BPOS 0.15% and Alphagan was made.

III. Study Results

Study 7 (190342-007):

Investigators from twenty-three study centers in the United States enrolled 593 patients between October 6, 1998 to September 20, 1999. One hundred ninety-seven patients were randomized to receive BPOS 0.15%, 197 patients were randomized to BPOS 0.2% group, and 199 patients were randomized to the Alphagan group. Based on the definition of ITT, all the patients randomized belonged to this analysis population. Five hundred eighty-four patients were included in the per protocol population: 194 in BPOS 0.15% group, 192 in BPOS 0.2% group and 198 in Alphagan group. Patient accounting information was summarized in Table 1-7.

Table 1-7: Patient accounting information for Study 7.

	BPOS 0.15%	**BPOS 0.2%**	**Alphagan**	**Total**
Randomized	197	197	199	593
Completed at 3 month	172 (87.3%)	172 (87.3%)	175 (87.9%)	519 (87.5%)
Discontinued	25 (12.7%)	25 (12.7%)	24 (12.1%)	74 (12.5%)
Lack of efficacy	8 (4.1%)	3 (1.5%)	3 (1.5%)	14 (2.4%)
Adverse events	11 (5.6%)	14 (7.1%)	19 (9.5%)	44 (7.4%)
Ocular	8 (4.1%)	11 (5.6%)	18 (9.0%)	37 (6.2%)
System	5 (2.5%)	4 (2.0%)	3 (1.5%)	12 (2.0%)
Protocol violation	1 (0.5%)	3 (1.5%)	0 (0.0%)	4 (0.7%)
Administrative	4 (2.0%)	4 (2.0%)	2 (1.0%)	10 (1.7%)
Other	1 (0.5%)	1 (0.5%)	0 (0.0%)	2 (0.3%)

Source: Table 1 in Section 14.1 page 70 vol.110.

Reviewer's comment: From Table 1-7, it can be seen there were more patients (4.1%) discontinued due to lack of efficacy in BPOS 0.15% treatment group before Month 3 than that in the other two treatment groups (1.5% for BPOS 0.2% and 1.5% for Alphagan treatment groups). The difference between BPOS 0.15% and Alphagan was not statistically significant (two sided p-value was 0.139 calculated by this reviewer).

Demographic and medical history information showed reasonable balances between treatment groups. Except in ophthalmic diagnosis, more patients (62.9%) in BPOS 0.15% diagnosed with glaucoma, while 58.4% patients in BPOS 0.2% and 51.8% in Alphagan were diagnosed with glaucoma. The difference was statistically significant with p-value 0.068.

Sponsor's efficacy results of primary endpoint:

The primary efficacy variable specified in the analysis plan was the change of IOP from baseline. For ITT analyses with LOCF, differences between treatment groups for IOP change from baseline at each time points were listed in Table 2-7. For the comparisons between BPOS 0.2% and Alphagan at the ten time points, all the upper limits of two-sided 95%CIs for the ten comparisons were within 1.5 mm Hg, while six of the upper limits were within 1.0 mm Hg. For the comparisons between BPOS 0.15% and Alphagan, at one time point, the upper limit of 95% CI at Month 3 Hour 9 exceeded 1.5 mm Hg equivalence limit, which was statistically significant at level 0.05. Four comparisons had the upper limit within 1.0 mm Hg.

Within each treatment groups, on average IOP was lowered more than 3 mm Hg from baseline.

In these analyses, two-way ANOVA models with treatment group, investigator center, as well as interaction term as covariates were used. Statistical significant center effects were observed in the analyses of IOP change from baseline. This was more likely attributed to the statistical significant baseline difference among centers. However, there was no consistent treatment by center interaction.

Comparisons of IOP at each time points in ITT population and per protocol analyses showed similar results to the analysis of change from baseline.

Table 2-7: IOP difference between treatment groups and 95%CIs for changes from baseline by time points for Study 7.

Time points	BPOS 0.15%-Alphagan	BPOS 0.2% - Alphagan	BPOS 0.15% - BPOS 0.2%
Week 2: hour 0	-0.27 (-0.94, 0.41)	0.15 (-0.52, 0.83)	-0.42 (-1.09, 0.26)
hour 2	0.52 (-0.16, 1.21)	0.67 (-0.02, 1.35)	-0.14 (-0.83, 0.54)
Week 6: hour 0	0.12 (-0.54, 0.79)	0.34 (-0.33, 1.00)	-0.21 (-0.88, 0.45)
hour 2	0.33 (-0.35, 1.01)	0.54 (-0.14, 1.22)	-0.21 (-0.89, 0.47)
hour 7	0.25 (-0.39, 0.89)	0.14 (-0.51, 0.78)	0.11 (-0.53, 0.76)
hour 9	0.46 (-0.27, 1.18)	0.28 (-0.44, 1.01)	0.17 (-0.55, 0.90)
Month 3 hour 0	-0.11 (-0.79, 0.57)	0.11 (-0.57, 0.79)	-0.22 (-0.90, 0.46)
hour 2	0.42 (-0.26, 1.10)	0.44 (-0.24, 1.12)	-0.02 (-0.07, 0.66)
hour 7	0.44 (-0.23, 1.10)	0.22 (-0.44, 0.88)	0.21 (-0.45, 0.88)
hour 9	0.92 (0.22, 1.63)*	0.28 (-0.42, 0.98)	0.64 (-0.06, 1.34)

* Statistically significant at 0.05.

Sources: based on section 10 Tables 14.2, 16.2, & 18.2 pages 107, 113, & 119 in Vol. 110.

Secondary analysis:

The rates of clinical success evaluated at Month 3 among the three treatment groups were similar. Patient satisfaction evaluation among the three treatment groups was also similar from baseline to Month 3 except the evaluation at Month 3. At Month 3, more patients in BPOS 0.15% group rated at least slightly satisfied (94.9%) than that in BPOS 0.2% (89.0%) and Alphagan (90.1%). P-value was 0.024 for the comparison of BPOS 0.15% vs. Alphagan.

Study 8 (190342-008):

Investigators from twenty-one study centers in the United States enrolled 554 patients between September 28, 1998 to September 9, 1999. One hundred eighty-four patients were randomized to receive BPOS 0.15%, 186 patients were randomized to BPOS 0.2% group, and 184 patients were randomized to the Alphagan group. Based on the definition of ITT, all the patients randomized belonged to this analysis population. Five hundred fourty-two patients were included in the per protocol population: 180 in BPOS 0.15% group, 183 in BPOS 0.2% group and 179 in Alphagan group. Patient accounting information was summarized in Table 1-8.

Table 1-8: Patient accounting information for Study 8

	BPOS 0.15%	BPOS 0.2%	Alphagan	Total
Randomized	184	186	184	554
Completed at 3 month	160 (87.0%)	159 (85.5%)	164 (89.1%)	483 (87.2%)
Discontinued	24 (13.0%)	27 (14.5%)	20 (10.9%)	71 (12.8%)
Lack of efficacy	7 (3.8%)	5 (2.7%)	1 (0.5%)	13 (2.3%)
Adverse events	12 (6.5%)	11 (5.9%)	14 (7.6%)	37 (6.7%)
Ocular	11 (6.0%)	8 (4.3%)	12 (6.5%)	31 (5.6%)
System	2 (1.1%)	3 (1.6%)	2 (1.1%)	7 (1.3%)
Protocol violation	2 (1.1%)	5 (2.7%)	2 (1.1%)	9 (1.6%)
Administrative	1 (0.5 %)	4 (2.2%)	0 (0.0%)	5 (0.9%)
Other	2 (1.1%)	2 (1.1%)	3 (1.6%)	7 (1.3%)

Source: Table 1 in Section 14.1 page 72 vol.134.

Reviewer's comment: From Table 1-8, it can be seen there were more patients (3.8%) discontinued due to lack of efficacy in BPOS 0.15% treatment group before Month 3 than that in the other two treatment groups (2.7% for BPOS 0.2% and 0.5% for Alphagan treatment groups). The difference between BPOS 0.15% and Alphagan was close to statistically significant at 0.05 level for two-sided p-value (p=0.067) according to this reviewer's calculation.

Demographic characteristics showed reasonable balances between treatment groups. The majority of medical history information was in balance except in gynecologic, post menopausal, endocrine and pruritus which had statistically significant imbalance among

treatment groups. Opposite to Study 7, less patients in BPOS 0.15% (56.0%) were diagnosed with glaucoma than that in BPOS 0.2% (68.8%) and in Alphagan (62.5%). The difference was close to statistical significant with p-value 0.086.

Sponsor's efficacy results of primary endpoint:

The primary efficacy variable specified in the analysis plan were the change of IOP from baseline. For ITT population with LOCF, differences between treatment groups for IOP change from baseline at each time points were listed in Table 2-8. For the comparisons between BPOS 0.2% and Alphagan at the ten time points, all the upper limits of two-sided 95%CIs of the ten comparisons were within 1.5 mm Hg, while three of the upper limits exceeded 1.0 mm Hg. For the comparisons between BPOS 0.15% and Alphagan, at Month 3 hour 2 and hour 9, Alphagan showed statistically significantly superior at level 0.05 to BPOS 0.15%, and the upper limit of the 95% CIs at two of the three time points were exceed 1.5 mm Hg. Of the 10 time points, the upper limits of 95% CIs exceeded 1.5 mm Hg at three time points (Week 6 Hour 2, Month 3 Hour 2 and Hour 9). Three comparisons had the upper limits within 1.0 mm Hg.

Within each treatment groups, on average IOP was lowered more than 3 mm Hg from baseline.

In these analyses, two-way ANOVA models with treatment group, investigator center, as well as the interaction term as covariates were used. Statistical significant center effects were observed in the analyses of IOP change from baseline. This was more likely attributed to the statistical significant baseline difference among centers. However, there was no consistent treatment by center interaction.

Per protocol analysis of IOP change from baseline presented consistent results as the ITT analysis. The comparison between BPOS 0.15% and Alphagan in mean IOP were within 1.5 mm Hg for all the upper limits of 95% CIs of the ten time points. The upper limits of the difference between BPOS 0.2% and Alphagan were all within 1.0 mm Hg at the ten time points.

Table 2-8: IOP difference between treatment groups and 95%CI for change from baseline by time points for Study 8.

Time points	BPOS 0.15%-Alphagan	BPOS 0.2% - Alphagan	BPOS 0.15% - BPOS 0.2%
Week 2: hour 0	0.23 (-0.37, 0.84)	0.40 (-0.20, 1.01)	-0.17 (-0.77, 0.44)
hour 2	0.66 (-0.07, 1.38)	0.03 (-0.68, 0.75)	0.62 (-0.09, 1.34)
Week 6: hour 0	0.45 (-0.16, 1.06)	0.50 (-0.10, 1.11)	-0.05 (-0.66, 0.55)
hour 2	0.76 (-0.01, 1.53)	0.14 (-0.62, 0.91)	0.62 (-0.14, 1.38)
hour 7	-0.08 (-0.79, 0.62)	-0.07 (-0.77, 0.64)	-0.02 (-0.72, 0.69)
hour 9	0.45 (-0.30, 1.20)	0.13 (-0.61, 0.87)	0.32 (-0.41, 1.06)
Month 3 hour 0	0.51 (-0.13, 1.15)	0.35 (-0.29, 0.98)	0.16 (-0.47, 0.80)
hour 2	0.92 (0.15, 1.69)*	0.12 (-0.65, 0.89)	0.80 (0.03, 1.57)*
hour 7	0.23 (-0.47, 0.93)	-0.05 (-0.75, 0.64)	0.28 (-0.42, 0.98)
hour 9	0.82 (0.05, 1.59)*	0.35 (-0.42, 1.11)	0.47 (-0.30, 1.24)

* statistically significant at level 0.05.
Sources: based on section 10 Tables 14.2, 16.2, & 18.2 pages 109, 134, & 121 in Vol. 134.

Secondary analysis:

The rates of clinical success evaluated at Month 3 among the three treatment groups were similar. Patient satisfaction evaluation among the three treatment groups was also consistently similar from baseline to Month 3.

Integrated efficacy analysis of Studies 7 and 8:

Sponsor's efficacy results of primary endpoint:

For integrated data set, there were no statistically significant differences among the treatment groups for demographic variables, ophthalmic diagnosis, and history of glaucoma medications.

For ITT population with LOCF, differences between treatment groups for IOP change from baseline at each time points were listed in Table 2. For the comparisons between BPOS 0.2% and Alphagan at the ten time points, all the upper limits of two-sided 95% CIs for the ten comparisons were within 1.0 mm Hg. For the comparisons between BPOS 0.15% and Alphagan, all the upper limits of two-sided 95%CIs for the ten comparisons were within 1.5 mm Hg, and at five of the ten time points, the upper limits were less than 1.0 mm Hg.

Table 2: IOP difference between treatment groups and 95%CI for change from baseline by time points (combining Studies 7&8).

Time points	BPOS 0.15%- Alphagan	BPOS 0.2% - Alphagan	BPOS 0.15% - BPOS 0.2%
Week 2: hour 0	-0.12 (-0.56, 0.32)	0.21 (-0.23, 0.66)	-0.33 (-0.78, 0.11)
hour 2	0.57 (0.08, 1.06)*	0.39 (-0.10, 0.88)	0.18 (-0.31, 0.67)
Week 6: hour 0	0.16 (-0.30, 0.61)	0.31 (-0.14, 0.76)	-0.15 (-0.60, 0.30)
hour 2	0.52 (0.01, 1.03)*	0.37 (-0.14, 0.87)	0.15 (-0.35. 0.66)
hour 7	0.06 (-0.42, 0.53)	0.08 (-0.40, 0.55)	-0.02 (-0.50, 0.45)
hour 9	0.54 (0.02, 1.06)*	0.23 (-0.29, 0.75)	0.31 (-0.21, 0.83)
Month 3 hour 0	0.12 (-0.33, 0.58)	0.20 (-0.26, 0.66)	-0.07 (-0.53, 0.39)
hour 2	0.69 (0.18, 1.20)*	0.31 (-0.20, 0.82)	0.38 (-0.13, 0.89)
hour 7	0.30 (-0.18, 0.77)	0.09 (-0.39, 0.57)	0.20 (-0.28, 0.68)
hour 9	0.90 (0.37, 1.42)*	0.29 (-0.24, 0.81)	0.61 (0.08, 1.13)*

* Statistically significant at level 0.05.
Sources: based on section 10 Tables 14.2, 16.2, & 18.2 pages 159, 165, & 171 in Vol. 98.

Subgroup analyses:

Age: patients were divided into two age groups, <65 years old and ≥65 years old. The proportions of patients in each age group were similar between treatment groups. In general, Alphagan showed better treatment effect compared to BPOS 0.2% and BPOS 0.15% numerically for age group ≥65 years old, especially at Month 3 Hour 9.

Gender: no gender effect was observed in subgroup analysis.

Race: black vs. non-black. Overall 13.4% of patients were black and 86.6% were non-black. Since the black population was relative small, it was difficult to assess the validity of analysis results derived from this subgroup.

Iris color: light vs. dark. The proportion of patients to each iris color group was similar across treatment groups. The iris color effect was quite large at time points Hour 9 in Week 6 and Month 3. At these time points, Alphagan was superior to BPOS 0.15% in light iris color subgroup.

IV. Reviewer's Comments:

1. Reviewer's analysis on primary endpoints:

This reviewer did a similar analysis using the primary endpoint by counting the center as random effect instead of fixed effect and without last observation carried forward. Similar results were obtained from the reviewer's analysis to the sponsor's analysis.

2. Discontinuation due to lack of efficacy:

Both Studies 7 and 8 had more patients discontinued treatment due to lack of efficacy in BPOS 0.15% treatment groups compared with that in Alphagan treatment group. Such differences were approaching statistical significant at level 0.05 in the two studies. Combining the two studies, the withdrawal rate due to lack of efficacy was 3.9% in BPOS 0.15% and 1.0% in Alphagan. The p-value for the comparison of BPOS 0.15% to Alphagan was statistically significant at level 0.05 (two sided p-value was 0.011). This analysis suggested that BPOS 0.15% was slightly inferior to Alphagan in lowering IOP.

V. Conclusion:

For BPOS 0.2%, the results of primary analysis on mean IOP change from baseline, the primary end point specified in sponsor's analysis plan, in each individual studies (Studies 7 and 8) consistently satisfied the evaluation criteria of therapeutic equivalence to Alphagan agreed by both the agency and the sponsor.

For BPOS 0.15%, neither study had met the evaluation criteria of therapeutic equivalence to Alphagan based on the analyses of primary end points. The analysis of withdrawal due to lack of efficacy showed that BPOS 0.15% was numerically inferior to Alphagan. However, the results of IOP change from baseline were close to the non-inferiority criteria. The differences of withdrawal rates due to lack of efficacy between BPOS 0.15% and Alphagan were only about 3%. The average change from baseline for BPOS 0.15% treatment group was more than 3 mm Hg for both studies. The integrated analysis of IOP change from baseline by pooling the two studies together marginally satisfied the equivalence criteria. To assess evidence collectively, the two studies showed that the efficacy of BPOS 0.15% was close to that of Alphagan, but somewhat inferior to Alphagan based on the results of the individual studies and criteria agreed upon by the agency and the sponsor.

/S/

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Concur:

/S/

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